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Some neuroprotective approaches in focal and global ischaemia on *in vivo* and *in vitro* rat models

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Glutamate (Glu) is the major excitatory amino acid neurotransmitter in the central nervous system. It mediates a number of physiological processes, but it is involved in the pathological processes of excitotoxicity too. Traumatic brain injury, focal brain lesion or global hypoperfusion are followed by acute excitotoxicity caused by the presence of abnormally high Glu levels in the cerebrospinal and interstitial fluids.

It has recently been demonstrated that this excess Glu in the brain can be eliminated by the intravenous administration of oxaloacetate (OxAc), which, by scavenging the blood Glu, induces an enhanced and neuroprotective brain-to-blood Glu efflux.

In this study, we subjected rats to a photothrombotic lesion and treated them after the illumination with a single 30-min long administration of OxAc (1.2 mg/100 g, i.v.). Following induction of the lesion, we measured the infarct size by Fluoro-Jade B (FJB)-staining. FJB binds sensitively and specifically to damaged neurons, with increased contrast during acute neuronal stress. Coronal sections (30μm) were cut with a freezing microtome and the sections were stained with FJB. The sections were subsequently analyzed with a fluorescent microscope. The volume of the hemispheric lesion and the number of FJB-positive cells were calculated for each animal. The administration of OxAc resulted in a reduction in the volume of the ischemia-induced cortical damage.

We also examined the functional consequences of the photothrombotic lesion by measuring the amplitudes of the somatosensory evoked potentials (SEPs). SEPs were induced in the contralateral primary somatosensory cortex by electrical stimulation of the right whisker pad and were transcranially recorded. The photothrombotic lesion resulted in appreciably decreased amplitudes of SEPs, but OxAc administration significantly attenuated this reduction.

We suggest that the neuroprotective effects of OxAc are due to its blood Glu scavenging activity, which, by increasing the brain-to-blood Glu efflux, reduces the excess Glu in the brain. This limits the size of the penumbra, improves the tissue perfusion and oxygenation and reduces the ischemia-related functional damage.

Ischemic postconditioning is referred to preventing ischaemia/reperfusion injury in both myocardial and cerebral infarction. The next study was undertaken to evaluate possible neuroprotective effects of kainate postconditioning against delayed neuronal death in hippocampal CA1 neurons if applied two days after hypoperfusion.

Transient global hypoperfusion was induced in male Wistar rats by two-vessel occlusion (2VO) for 30 min. 2VO causes inhibition of protein synthesis in selectively vulnerable brain regions such as CA1 and leads to the decrease of dendritic spine number and resulted in an impaired long-term potentiation (LTP) function in the hippocampal CA1 region.

In order to determine the number of apical dendritic spines we used Golgi-Cox staining. When the impregnation was ready coronal brain sections were cut by vibratome. The clear Golgi sections have been evaluated by light microscopical stereology.

For electrophysiological recordings we prepared coronal slices from the middle part of hippocampi. Field excitatory postsynaptic potencials (fEPSPs) were monitored and after a control period, LTP of the Schaffer collateral-CA1 synaptic response was induced by high-frequency stimulation (HFS). After the HFS the fEPSPs were recorded for at least a further 60 min-long period. If we apply the kainate (5 mg/kg) 48 hours after the 2VO, the loss of hippocampal dendritic spines and dysfunction of LTP could be significantly averted.

These results suggest that a sublethal second post-ischaemic event can be considered as a trigger for the start of protein synthesis activity in post-ischaemic cells. Postconditioning probably causes a re-modulation of protective protein (hsp70, hsp72, Bcl-2) synthesis leading to a switch from pro-apoptotic to anti-apoptotic pathways.

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